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RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1615

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Walter MUELLER, et al.
Serial No.	:	09/647,290
Filed	:	November 28, 2000
For	:	TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF
Group Art Unit	:	1615
Examiner	:	Isis A. D. Ghali

Bef 4-24-03

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April 22, 2003
C. Bruce Hamburg

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE AFTER FINAL REJECTION UNDER 37 CFR 1.116

Sir:

In response to the Office Action of November 1, 2002, the rejections are respectfully traversed as follows:

Claim Rejections based on 35 U.S.C. § 102 (NOVELTY)

CHIANG et al., Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 22 (1995) 710-711

CHIANG is discloses a) a "simple matrix system" and b) a "two-phase matrix system".

A) The Simple Matrix System of CHIANG

CHIANG discloses the manufacture of a **simple matrix system** as follows: "N-0923 was dispersed or dissolved in vehicles, then mixed with pressure sensitive adhesives to form a uniform adhesive mixture. This mixture was cast onto a release film. The cast film was then dried at 70°C for 30 minutes. A polyester film was laminated onto the casting film as a backing layer." (p. 710. left column, paragraph "Experimental", l. 2-9)

Applicants understanding of the meaning of the term "or" in the first sentence of this disclosure is that N-0923 is used generally in combination with a "vehicle". Depending on the specific solubility properties of these vehicles, N-0923 is "dissolved" or "dispersed". The condition "dissolved" stands for a complete dissolution of N-0923 in the vehicle; the condition "dispersed" connotes the

existence of additional undissolved N-0923 in the vehicle, thereby giving a dispersion.

The three types of "vehicle" which have been used are specified in the sentence bridging p. 710 and p. 711: "The binary combination, benzyl alcohol (BA)/Propylene glycol monolaurate(PGML) ... [and] ... the ternary combinations, buffer/PG/PGML and BA/PG/PGML ...". PG appears to be the abbreviation for propylene glycol, see p. 710, left column, line 8 from bottom. The buffer is "a pH 6.0 phosphate buffer", see p. 710, right column, paragraph "Release Study", line 6-7.

In addition to those "optimized liquid vehicles saturated with N-0923", N-0923 was "incorporated" into various polymers in the form of a "powder" (p. 711, left column, paragraph "Skin flux studies", l. 1-3), i. e. without any vehicle.

The construction of the simple matrix systems of CHIANG which can be produced accordingly, is as follows: a) a backing layer, b) an adhesive layer and c) a release film, wherein the adhesive layer consists of N-0923 and a pressure sensitive adhesive – with or without a "vehicle".

An important part of the paper of CHIANG is the disclosure of the skin flux characteristics of some specific simple matrix systems which are summarized in

Table 1. It can be seen that the first three patches are based on a silicone adhesive, a polyisobutylene adhesive and an acrylate adhesive, each of which contains 10% or 30% of a solution of saturated N-0923 in pH 6 buffer, BA, PG and PGML. The fourth and fifth system are made of a silicone adhesive or a polyisobutylene adhesive and 3% or 6% of N-0923 as a powder, but without vehicle.

The skin flux of the last mentioned systems with N-0923 free of vehicle is 0.2 $\mu g/cm^2/hr$. The skin flux of systems with saturated solutions of vehicle is between 0.1 and 1.4 $\mu g/cm^2/hr$. This shows that the skin flux for the vehicle containing systems is much higher than the skin flux of the vehicle-free systems.

However, even a flux rate of 1.4 $\mu g/cm^2/hr$ is far less than the flux rate of 10-15 $\mu g/cm^2/hr$ which is the estimated delivery rate from a 20 cm^2 patch (confer p. 710, left column, second paragraph, l. 5-6) for an effective treatment of Parkinson's disease.

Thus it can be concluded that the simple matrix system of CHIANG with 3% or 6% of N-0923 as a powder and without any vehicle is absolutely unsuitable for transdermal delivery. In addition, the simple matrix system of CHIANG containing 10% or 30% of a solution of saturated N-0923 in an optimized vehicle is insufficient for an effective transdermal delivery.

The explanation which is given by CHIANG for this behaviour is "the difficult diffusion of the hydrophilic N-0923 compound from the hydrophobic polymers." (p. 711, left column, fourth paragraph, l. 9-11). It should be emphasized that CHIANG is pointing to the hydrophilic nature of N-0923 which clearly shows that a form of the specific drug is employed which has a good solubility in water but no good solubility in the hydrophobic polymers.

The difference between the simple matrix system of CHIANG and the transdermal therapeutic system of the present application is:

CHIANG / simple matrix system	present application
contains N-0923 as a hydrophilic compound, i. e. as a asalt	contains N-0923 as the **free base**
the hydrophobic adhesive has essentially no solubility for the hydrophilic compound	the hydrophobic adhesive has a **solubility** ≥ 5% for the free base
insufficient flux rates	sufficient flux rates

The differentiating features of claim 18 are printed in bold-face.

B) The Two Phase Matrix System of CHIANG

CHIANG discloses the manufacture of a **two-phase matrix systems** as follows: "N-0923 was dissolved in a mixture of phosphate buffer, propylene glycol and benzyl alcohol. The dissolved N-0923 solution was then added to Micro-Cel E and mixed vigorously to form a viscous hydrophilic mixture. Tween 20, propylene glycol monolaurate and silicone adhesive were added to the hydrophilic mixture and resulted in a finely dispersed mixture. This mixture was then cast onto a release film, and the solvent was evaporated. A polyester film was then laminated onto the film." (p. 710. left column, paragraph "Experimental", l. 10 to right column, l. 3)

The construction of the two-phase matrix systems of CHIANG which can be produced accordingly, is as follows: a) a backing layer, b) an adhesive layer and c) a release film. The adhesive layer consists of N-0923, a phosphate buffer, propylene glycol, benzyl alcohol, Micro-Cel E, Tween 20, propylene glycol monolaurate and a silicone adhesive.

Note: Micro-Cel E is a synthetic calcium silicate; Tween 20 is polyoxyethylene(20)-sorbitane monolaureate, a water-soluble detergent which serves as solubility enhancer.

Additionally, applicants would like to emphasize the fact that by the addition of Tween 20, PGML and silicone adhesive to the "dissolved solution" a "finely dispersed mixture" is obtained.

This clearly shows the presence of a two phases that are immiscible. In addition, is should be kept in mind that the presence of a phosphate buffer is strictly bound to the concomitant presence of water.

Thus, the difference between the simple matrix system and the two-phase matrix system of CHIANG is the nature of the adhesive layer. While in the simple matrix system N-0923 is contained as a powder or as a saturated solution in a vehicle within the hydrophobic adhesive, in the two phase matrix system N-0923 is contained in a separate hydrophilic phase that is incorporated within the adhesive.

In this two phase matrix system the hydrophilic phase contains virtually all hydrophilic components and the hydrophobic phase contains virtually all hydrophobic components. This complies with the general rule "similia similibus solvuntur" which means that the solubility of nonpolar (hydrophobic) compounds in nonpolar (hydrophobic) solvents is greater than in polar (hydrophilic) solvents, and vice versa. To that extent, it is correct when the Examiner states that "The solubility of particular drug in particular adhesive is inherent."

As a consequence of this general rule, it is emphasized that the hydrophilic phase of the two phase system of CHIANG contains N-0923, the phosphate buffer, propylene glycol, benzyl alcohol, Micro-Cel E, Tween 20, and propylene glycol monolaurate, while the hydrophobic phase consists virtually solely of the silicone adhesive.

The skin flux characteristics of some specific two phase matrix systems are summarized in Table 2. It can be seen that two of the four samples have a delivery rate of greater than 10 $\mu g/cm^2/hr$, indicating a sufficient skin flux.

This behavior is explained by CHIANG "with the incorporation of a hydrophilic phase into the adhesive" (p. 711, right column, l. 3-4) and the subsequent development of a two-phase system. It derives undoubtedly from this statement that the "hydrophilic N-0923 compound" is contained in the "hydrophilic phase" and that the hydrophilic N-0923 compound has a good solubility in the aqueous phase. This clearly demonstrates the presence of N-0923 as a salt.

The difference between the two phase matrix system of CHIANG and the transdermal therapeutic system of the present application is:

CHIANG / two phase matrix system	present invention
two phase matrix system	single matrix system
N-0923 as a hydrophilic compound, i. e. as a salt is dissolved in the hydrophilic phase	N-0923 as the **free base** dissolved in the hydrophobic polymer having a solubility ≥ 5%
containing MicroCel E, a synthetic calcium silicate	free of calcium silicate
aqueous due to the presence of MicroCel E and phosphate buffer pH 6	**non-aqueous**

The differentiating features of claim 18 are printed in bold-face.

WO 94/07468 (Cygnus Therapeutics)

This PCT application discloses a two phase matrix system. The Examiner's statement "a transdermal drug delivery device comprising a matrix containing the drug in a polymer base" is inaccurate. In fact, the matrix comprises "(a) a continuous hydrophobic polymer phase; (b) a particulate phase dispersed in the continuous polymer phase comprised of: (i) a hydrated inorganic silicate; (ii) a water-solubilizable drug at least partially dissolved in the aqueous phase of (i); and (c) a dispersing agent for dispersing (b) in (a)" (p. 3, l. 15-22).

Thus, the matrix does not contain the drug in a polymer base. In contrast to the position of the Examiner, the drug is dissolved in an aqueous phase of a hydrated inorganic silicate which is a phase based on particles that are dispersed in a said polymer phase. The WO states that "correlatively, the drug is substantially insoluble

in the hydrophobic polymer component of the matrix and hence no significant amount of drug is dissolved in that polymer." (p. 7, l. 21-23).

The Examiner, while stating that the silicone-based or acrylate-based polmers have a "solubility of drugs less than 1%" is exactly pointing to the difference between the disclosure of WO 94/07468 and the present application. Applicants polymers have a solubility for N-0923 **greater or equal than 5%**, as claimed in claim 18. For this reason applicants believe it is incomprehensible why the Examiner is citing WO 94/07468 as prior art under 35 U.S.C. 102(b).

Claim Rejections based on 35 U.S.C. § 103 (OBVIOUSNESS)

The technical background

The name N-0923 is an abbreviation used for the hydrochloride salt of (–)-S-2-(N-propyl-N-2-thienylethylamino)-5-hydroxy tetralin. Other names for this compound are (–)-5-Hydroxy-2[*N*-n-propyl *N*-2-(2-thienyl)ethylamino]tetralin hydrochloride and (–)-5,6,7,8-Tetrahydro-6-[propyl-[2-[2-thienyl)ethyl]amino]-1-naphthalenol hydrochloride.

This "Nelson code number" is referenced in "DMF Type II: N-0923 – Section II: Drug Substance" and an "Analytical Chemistry Report" of Nelson Research & Development Co. (attached hereto). The DMF Type II clearly shows that the CAS registry number 102120-99-0 concerns N-0923 (i. e. the hydrochloride salt) and the CAS registry number 99755-59-6 "N-0923 free amine".

Thus, the fact that the abbrevation N-0923 is used by CHIANG without the specific indication that the "free amine" (i. e. the free base form) is used, evidences for the fact that CHIANG uses the hydrochloride salt.

In this context it should be recalled that the present specification has been misunderstood by the Examiner when stating: "...that both the drug and the hydrochloride salt can be used." In the event that the hydrochloride salt is employed, an auxiliary substance shall be used. These auxiliary substances do have the function to convert the hydrochloride salt into the free base form of the drug: "An auxiliary substance which advantageously is added to the active substance solution directly is, for example, an alkaline substance which is suitable for **converting** the active substance **hydrochloride into** the **free** active substance **base.**" [emphasis added] In this manner it is ensured that the hydrochloride salt is not contained in the matrix layer.

EXAMINER'S POSITION to Applicants arguments:

Statement: "CHIANG does not teach anywhere hydrochloride salt of (-)-5,6,7,8-tetrahydro-6[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphtalenol."

It is correct that CHIANG does not explicitly use the term "hydrochloride salt". However, as shown, the term N-0923 is used for the hydrochloride salt of (-)-5,6,7,8-tetrahydro-6[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphtalenol. Thus, if CHIANG would not have used the hydrochloride salt of (-)-5,6,7,8-tetrahydro-6[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphtalenol, he would have used the term "free amine of N-0923".

The fact that CHIANG is explicitely pointing to the "hydrophilic N-0923 compound" is a further evidence that the hydrochloride of (-)-5,6,7,8-tetrahydro-6[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphthalenol is used.

Therefore, it is applicants position that the Examiner is in error with respect to the disclosure of CHIANG.

Statement: "Claim language permits the presence of particulate hydrophilic material."

Originally, the feature concerning the "particulate hydrophilic material" was disclaimed by the term "substantially free of". However, this disclaimer has been deleted in claim 18 because of insufficient clarity and because of an undue limitation of the scope of the invention.

The technical feature which is in claim 18 that excludes the presence of a hydrophilic phase within the adhesive layer is in the term "non-aqueous". It is applicant's position that the property "non-aqueous" which is conterminous with "free of water", is a garantuee for firstly the presence of the free base form of N-0923 in the adhesive layer and secondly the absence of an additional hydrophilic phase.

Statement: "It is within the skill of the art to select the matrix system."

As clearly indicated by the examples in the prior art, the desired flux rates or dose needed can not be gained with "simple matrix systems". However, in contrast to the teaching of the prior art, the present invention is based on applicants' discovery that a sufficient flux can be obtained by a simple matrix system, if the "free base" of N-0923 is used and contained in an adhesive having "a solubility of ≥ 5%". The combination of these two features cannot be derived by combining or modifying the prior art.

A three month extension of time for responding to the Office Action is hereby requested. Please charge the fee of $930 for the extension of time to Deposit Account No. 10-1250. Also, please charge any deficiency or credit any overpayment to Deposit Account No. 10-1250.

Respectfully submitted,

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